Science of the Total Environment 616–617 (2018) 1134–1138

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Ambient temperature and hospital admissions for acute kidney injury: A time-series analysis

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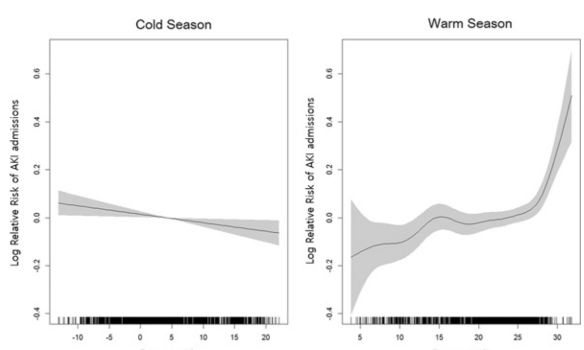
HIGHLIGHTS

- High temperature and acute kidney injury have a strong relationship.
- A nonlinear relationship with a flexion point was observed in the warm season.
- Men with hypertension were most vulnerable to high ambient temperatures.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 25 May 2017
Received in revised form 24 September 2017
Accepted 20 October 2017
Available online 28 October 2017

Editor: Scott Sheridan

Keywords:
Climate change
Health effect
Hot temperature
Vulnerable population

ABSTRACT

Some studies have suggested that high ambient temperatures are a risk factor for kidney-related diseases. However, none have examined the association between ambient temperature and acute kidney injury (AKI). This study aimed to examine the association between daily mean temperature and AKI and identify high-risk subgroups in this association. We obtained health insurance claim data from the Health Insurance Review and Assessment Service (HIRA) for 24,800 admitted cases of AKI during the period 2007–2014 in Seoul, Korea. Using a time-series design and piecewise linear regression models, we estimated the percentage change in AKI admissions associated with daily mean temperature after controlling for relevant covariates. Daily mean temperature and AKI admissions displayed an inverse association in the cold season and a nonlinear relationship with a flexion point around 28.8 °C in the warm season. AKI admissions increased by 23.3% (95% confidence interval [CI]: 14.3, 33.0) per 1 °C increase in mean temperature above the 28.8 °C flexion point in the warm season. The estimates were greatest among men with hypertension (55.1%; 95% CI: 25.1, 92.2). However, we did not observe significant increases in AKI admissions associated with ambient temperature in the cold season (0.4% [95% CI: −0.1, 0.9] per 1 °C decrease in mean temperature). Our results suggest that hospital admissions for AKI increase in association

Abbreviations: CI, confidence interval; AKI, acute kidney injury; HIRA, Health Insurance Review and Assessment Service; ICD-10, International Classification of Diseases Revision 10; AIC, Akaike Information Criterion.

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https://doi.org/10.1016/j.scitotenv.2017.10.207
0048-9697/

with high temperature, particularly among men with hypertension in the warm season. Thus, early detection of AKI during heat wave periods is crucial. Our findings also provide evidence for the local government to target populations vulnerable to high ambient temperatures.

1. Introduction

The rise in annual average ambient temperatures has been associated with increased prevalence of kidney-related diseases. Brikowski et al. (2008) discovered that global warming is a risk factor for kidney stone formation, or nephrolithiasis, and one of the plausible mechanisms for this is water loss via heat-induced sweating (Schrier et al., 1970).

While chronic dehydration is an important risk factor for nephrolithiasis, severe acute dehydration can cause acute kidney injury (AKI) (Brikowski et al., 2008; García-Trabanino et al., 2015). The risk of nephrolithiasis imposed by chronic dehydration can be worsened by comorbid conditions such as hypertension. Studies have suggested that hypertension may increase the risk of nephrolithiasis, likely due to abnormalities in renal calcium metabolism (Borghi et al., 1999) and abnormal renal pressure natriuresis, particularly in cases of obesity-related hypertension (Hall et al., 2003).

AKI occurs in 1% of patients newly admitted to the hospital and in 20% of patients admitted to intensive care units; the associated mortality is 15–60% (Albright, 2001; Liaño et al., 1996; Uchino et al., 2005). As small changes in renal function can influence patient outcomes, early detection and treatment of AKI are crucial (Lameire et al., 2013).

Considering that global warming leads to greater temperature variability (either extremely high or extremely low temperatures) that may result in dehydration (Lim et al., 2015), there is a need to investigate the relationship between temperature and AKI. Using health insurance claim data, we estimated the effect of ambient temperature on hospital admissions for AKI. To identify subgroups vulnerable to high or low temperatures, we compared temperature effects stratified by age and sex. Furthermore, given that kidney function could be adversely affected by hypertension, a stratified analysis of the association between ambient temperature and AKI was conducted based on the presence or absence of preexisting hypertension.

2. Methods

2.1. Study population

This study analyzed hospital admission data from Seoul during the period 2007–2014. Seoul is the largest city in Korea with a population of approximately 10 million. Hospital admission data were collected from the database of the Health Insurance Review and Assessment Service (HIRA), which covers 97% of Korea's population. AKI cases were defined as patients residing in Seoul who were first admitted to a hospital because of AKI between 2007 and 2014. The diagnosis of AKI was based on the primary and secondary disease codes of the International Classification of Diseases 10th Revision (ICD-10). Patients with ICD-10 code N17 were considered to have AKI. We excluded patients with both chronic kidney disease (ICD-10 code N18) and AKI because the underlying pathophysiological mechanisms of the acute exacerbations of chronic kidney disease might be different from those of AKI in subjects without chronic kidney disease.

For the stratified analysis, daily counts of hospital admissions were categorized by age (<75 years and ≥75 years), sex (male and female), and comorbid hypertension (with and without hypertension). Age was determined at the time of admission for AKI. Comorbid hypertension status was defined as “with hypertension” if the patient had visited a doctor's office or had been admitted to the hospital with ICD-10 codes I10 or I11 prior to the AKI events, or “without hypertension” if they did not fulfill these criteria.

As this study used de-identified publicly available data, the Seoul National University Hospital Institutional Review Board (IRB) deemed it exempt from IRB review (IRB No. H-1507-162-692).

2.2. Environmental variables

Hourly meteorological data were obtained from the Korea Meteorological Administration. Daily mean temperature (in degrees Celsius), relative humidity (in percentages), and sea-level air pressure (in hectopascals [hPa]) were recorded based on a 24-h period. The daily mean temperature was computed by averaging the hourly temperature measured in Jongno-gu (in the middle of Seoul) over the 24-h period.

2.3. Statistical analysis

We used a time-series analysis of the hospital admissions for AKI. The associations between ambient temperature and AKI were visualized using a generalized additive model (Wood, 2001). To estimate the effects of temperature on AKI admissions in each season, we divided the data into two seasons during the period 2007–2014: cold season from October to March of the following year and warm season from April to September. Because temperature and AKI admissions displayed an inverse association in the cold season, we used generalized linear modeling to estimate the relative risk of low temperature after controlling for day of the week, daily mean relative humidity, daily mean air pressure, and time trend. Meanwhile, as a nonlinear association was observed between AKI admissions and temperature in the warm season, a piecewise linear regression analysis was conducted to determine the temperature flexion point and estimate temperature effects below or above that flexion point. This analysis was performed using the HEAT package in R (Lim et al., 2013). The estimation of the flexion point was described in detail in our previous study (Lim et al., 2015). Briefly, we compared several models applying various flexion points within certain temperature ranges (e.g., 20–30 °C in the warm season) and determined the best model based on the Akaike Information Criterion (AIC) (Akaike, 1974). The model was given by

$$E(Y) = \beta_0 + \beta_1 \times \mathit{temperature} + \beta_2 \times (\mathit{temperature} - \xi)_+ + Z,$$
where $(\mathit{temperature} - \xi)_+ = \max\{\mathit{temperature} - \xi, 0\}$ and Z is a vector of covariates,

and where ξ is a temperature flexion point (e.g., in the range 20–30 °C in the warm season) and the covariates were day of the week, daily mean relative humidity, daily mean air pressure, and time trend. To investigate the delayed effects of temperature on AKI admissions, we examined lag days up to 2 weeks. We selected lag 0–1 (a moving average of 2 consecutive days' daily temperature) and lag 0 (concurrent day) in the cold and warm seasons, respectively, based on the lowest unbiased risk estimator of the generalized additive model (Wood, 2001) (Supplementary Fig. S1). We used 4 degrees of freedom (*df*) per year for the smoothing plots of time trend and expressed the estimates as percentage changes in AKI admissions per 1 °C temperature decrease and increase in the cold and warm seasons, respectively.

We estimated the temperature effects on AKI admissions by subgroups to identify vulnerable populations (based on age, sex, and comorbid hypertension) given the flexion point of temperature associated with total AKI admissions. Moreover, we tested for

significant differences between subgroups (e.g., patients with hypertension vs. patients without hypertension) by calculating 95% confidence intervals (CIs) (Payton et al., 2003; Schenker and Gentleman, 2001) as shown below:

$$\hat{Q}_1 - \hat{Q}_2 \pm 1.96 \times \sqrt{\hat{SE}_1^{\,2} + \hat{SE}_2^{\,2}}.$$

All statistical analyses were conducted using R version 3.2.3 (The Comprehensive R Archive Network, http://cran.r-project.org).

3. Results

During the period 2007–2014 in Seoul, 24,800 patients were hospitalized due to AKI: 12,706 in the warm season and 12,094 in the cold season. Table 1 shows the characteristics of these patients: 56.6% were male and 35.5% were elderly (≥75 years old). Diseases accompanying AKI at the time of admission were cardiovascular diseases (16.2%); endocrine, nutritional, and metabolic diseases (12.2%); malignant neoplasms (12.1%); genitourinary system diseases (11.7%); and infectious and parasitic diseases (11.0%). Specifically, diabetes and hypertension (6.8% and 5.1%, respectively) most commonly accompanied AKI at the time of admission (Supplementary Table S1). The daily mean number of AKI admissions was 8.5 overall, 8.7 in the warm season, and 8.3 in the cold season (all with a standard deviation of 3.7). The annual mean temperature was 12.7 °C, and the mean temperatures in the cold and warm seasons were 4.3 °C and 21.1 °C, respectively (Table 2).

AKI admissions and daily mean temperature at lag 0 showed linearly increasing associations, with an increase or decrease in temperature at extremely high or low temperatures, respectively; however, the fluctuations in the associations were observed between −5 °C and 15 °C (Supplementary Fig. S2). Particularly, the mean temperature and AKI admissions showed an inverse relationship in the cold season at lag 0–1 days (Fig. 1a) and a nonlinear relationship with a temperature flexion point in the warm season at lag 0 (Fig. 1b). Men, the elderly, those with hypertension, and men with hypertension had lower temperature flexion points in the warm season than the corresponding opposing groups (i.e., women, the young, those without hypertension, and women with hypertension, respectively) (Supplementary Fig. S3). However, we did not observe distinct patterns of low-temperature effects in the stratified subgroup analyses (Supplementary Fig. S4).

The effects of ambient temperature on AKI admissions in the cold and warm seasons are shown in Tables 3 and 4. The inverse association in the cold season showed a small increase in risk (0.4% [95% CI: −0.1, 0.9] per 1 °C decrease in daily mean temperature) (Table 3). The estimated risk of AKI admissions above the flexion point (28.8 °C) in the warm season increased by 23.3% (95% CI: 14.3, 33.0) per 1 °C increase in daily mean temperature, whereas the change in risk below the flexion point in the warm season was smaller (0.9% [95% CI: 0.4, 1.4]) (Table 4). The estimates for men were slightly greater than those for women in the warm season, particularly with ≥28.8 °C (28.3% for men vs. 16.0% for women); however, the difference was not significant at $\alpha = 0.05$. Similarly, we did not observe significant differences in the estimates stratified by age.

Table 2
Summary statistics of meteorological variables for the period 2007–2014.

Variable	Season	Mean ± SD
Mean temperature (°C)	Overall	12.7 ± 10.6
	Warm	21.1 ± 3.7
	Cold	4.3 ± 3.7
Mean relative humidity (%)	Overall	60.6 ± 14.9
	Warm	65.1 ± 14.8
	Cold	56.1 ± 13.5
Mean air pressure (hectopascals)	Overall	1016.0 ± 8.2
	Warm	1010.0 ± 5.5
	Cold	1022.1 ± 5.5

Fig. 2 shows the effects of high temperature on AKI admissions stratified by comorbid hypertension. Patients with preexisting hypertension were correlated with a greater increase in AKI admissions associated with ambient temperatures ≥28.8 °C than did those without hypertension (33.1% [95% CI: 10.7, 60.1] vs. 22.2% [95% CI: 12.6, 32.6], respectively), although the difference was not significant at $\alpha = 0.05$. Among those with preexisting hypertension, the effect of temperature on AKI admissions differed significantly by sex (55.1% [95% CI: 25.1, 92.2] for men with hypertension vs. −3.1% [95% CI: −33.9, 41.9] for women with hypertension, P-value for difference < 0.05).

4. Discussion

This is the first study to examine the association between temperature and AKI using health insurance claim data covering most Seoul residents. In Seoul, the number of hospital admissions for AKI exhibited a nonlinear relationship with ambient temperature in the warm season and an inverse association with ambient temperature in the cold season. Particularly, AKI admissions were significantly associated with temperatures above a flexion point of 28.8 °C in the warm season. Among AKI patients, men with comorbid hypertension were most vulnerable to high ambient temperatures.

Our findings suggest that high temperatures are associated with AKI admissions, consistent with the findings of previous studies that examined kidney-related diseases. Tasian et al. (2014) examined the association between nephrolithiasis and daily temperature in the US and suggested a strong association comparing daily temperatures of 30 °C vs. 10 °C for lags of ≤3 days. Similarly, in Seoul, Lee et al. (2016) demonstrated a cumulative relative risk of urolithiasis for a 20-day period comparing temperatures of 29 °C and 13 °C.

We have observed that the flexion points differed by age, sex, and presence of comorbid hypertension in the warm season (Supplementary Fig. S3) and were lower for men, the elderly, and those with

Table 1
Characteristics of patients hospitalized with acute kidney injury.

	Total		Without comorbid hypertension		With comorbid hypertension	
	n (%)	Daily number of AKI admissions (mean ± SD)	n (%)	Daily number of AKI admissions (mean ± SD)	n (%)	Daily number of AKI admissions (mean ± SD)
Total	24,800 (100)	8.5 ± 3.7	21,532 (100)	7.4 ± 3.3	3617 (100)	1.2 ± 1.2
Sex						
Male	14,027 (56.6)	4.8 ± 2.6	12,306 (57.2)	4.2 ± 2.3	1909 (52.8)	0.7 ± 0.8
Female	10,773 (43.4)	3.7 ± 2.2	9226 (42.8)	3.2 ± 2.0	1708 (47.2)	0.6 ± 0.8
Age						
<75 years	15,992 (64.5)	5.5 ± 2.7	14,082 (65.4)	4.8 ± 2.5	2090 (57.8)	0.7 ± 0.9
≥75 years	8808 (35.5)	3.0 ± 2.0	7450 (34.6)	2.5 ± 1.8	1527 (42.2)	0.5 ± 0.7
Season						
Warm (Apr–Sep)	12,706 (51.2)	8.7 ± 3.7	11,032 (51.2)	7.5 ± 3.3	1840 (50.9)	1.3 ± 1.2
Cold (Oct–Mar)	12,094 (48.4)	8.3 ± 3.7	10,500 (48.8)	7.2 ± 3.3	1777 (49.1)	1.2 ± 1.2

AKI, acute kidney injury; SD, standard deviation.

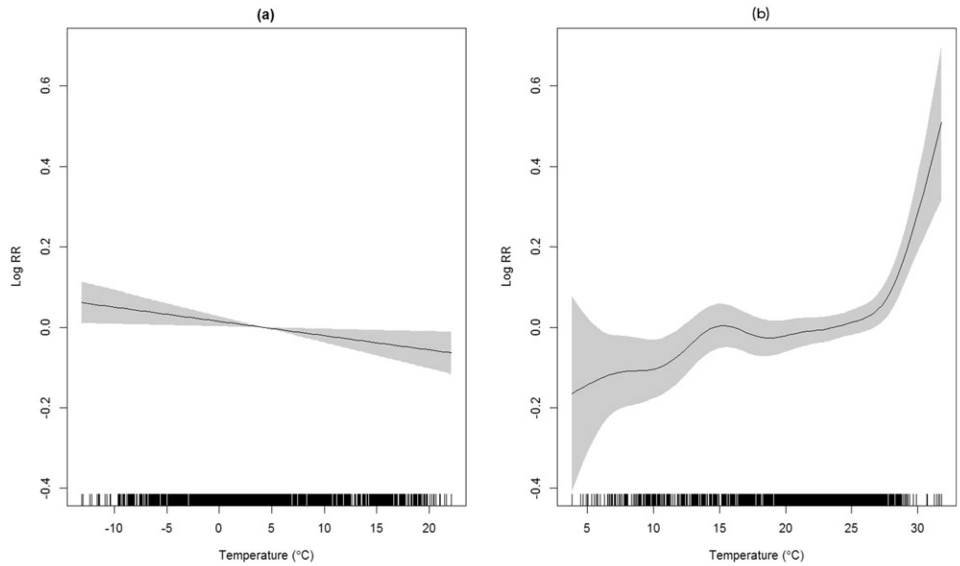

Fig. 1. Relationship between temperature and acute kidney injury admissions in Seoul by season during the period 2007–2014. (a) Cold season: October–March. (b) Warm season: April–September.

hypertension (particularly men) than for the corresponding groups (difference of ≥1 °C). This may imply synergistic effects between temperature and the status of the individual at the time of exposure (e.g., age, sex, and comorbidity), resulting in greater vulnerability to mild temperature changes and consequent hospitalization. However, the mechanism behind men, particularly men with hypertension, being more vulnerable to AKI in response to heat remains unclear. Further studies on lifestyle factors (alcohol consumption, smoking, and outdoor physical activity) of patients with AKI are thus necessary.

While previous studies suggested delayed effects of high temperature on kidney-related diseases, we observed more acute effects of high temperature on AKI (lag 0). We therefore postulate that high temperature causes nephrolithiasis and AKI via different pathophysiological pathways. Dehydration caused by high temperature may increase the supersaturation of calcium and uric acid, thereby promoting calcium stone formation on apatite deposits; it may take a few days before pain develops and the problem is noticed (Tasian et al., 2014). In contrast, the development of AKI due to hemodynamic derangement resulting from acute dehydration may be more rapid and may lead to immediate hospitalization.

This study has some limitations. First, the diagnosis of AKI can sometimes be missed by physicians because of the vague manifestations of mild AKI and lack of awareness by patients. This misclassification may lead to false negatives. Given this limitation, the study was conservatively conducted but still found significant associations. Moreover, we have not identified the severity and types of AKI such as pre-renal, intrinsic, or post-renal injury because we were unable to review the medical charts written by the physicians. Detailed information regarding diagnoses may well elucidate a dose-response relationship between the severity of AKI and ambient temperature. Second, misclassification of exposure was possible. Although most patients resided within 15 km from the meteorological station, we have not obtained information on activity and water intake during high- or low-temperature days, and available cooling systems in summer and heating systems in winter. This misclassification may bias our estimates toward the null hypothesis. Lastly, our small number of cases per day (<10) in the subgroup analysis indicates statistical instability. Therefore, a study with a larger population is required to confirm our findings.

5. Conclusions

This study suggests a significant association between ambient temperature and AKI admissions; men with comorbid hypertension were particularly susceptible to the effects of high temperature. As temperatures increase globally, there is a greater chance of having high-temperature days and, consequently, a higher chance of dehydration and increased incidence of AKI. Therefore, early detection and management of AKI (such as adequate hydration and avoidance of nephrotoxic drugs) by physicians or healthcare providers, particularly during heat

Table 3
Percentage change in the risk of acute kidney injury admissions per 1 °C decrease in temperature in the cold seasons.

	% change in AKI admissions	P-value
Total	0.4 (−0.1, 0.9)	0.1534
Sex		
Male	0.2 (−0.4, 0.9)	0.5052
Female	0.6 (−0.2, 1.3)	0.1569
Age		
<75 years	0.5 (−0.1, 1.1)	0.1278
≥75 years	0.1 (−0.7, 1.0)	0.7329
Hypertension status		
Without hypertension	0.5 (0.0, 1.1)	0.0656
With hypertension	−0.3 (−1.7, 1.0)	0.6263

Models controlled for day of the week, daily mean relative humidity, daily mean air pressure, and time trend. AKI, acute kidney injury.

Table 4
Percentage change in the risk of acute kidney injury admissions per 1 °C temperature increase in the warm seasons, stratified by baseline temperatures <28.8 °C and ≥28.8 °C.

	% change in AKI admissions			
	<28.8 °C		≥28.8 °C	
	% (95% CI)	P-value	% (95% CI)	P-value
Total	0.9 (0.4, 1.4)	0.0005	23.3 (14.3, 33.0)	<0.0001
Sex				
Male	1.0 (0.4, 1.7)	0.0026	28.3 (16.6, 41.2)	<0.0001
Female	0.7 (0.0, 1.5)	0.0640	16.1 (2.7, 31.3)	0.0174
Age				
<75 years	0.9 (0.3, 1.5)	0.0060	23.3 (12.0, 35.8)	<0.0001
≥75 years	0.9 (0.1, 1.8)	0.0296	23.3 (9.2, 39.2)	0.0007
Hypertension status				
Without hypertension	0.9 (0.4, 1.4)	0.0011	22.2 (12.6, 32.6)	<0.0001
With hypertension	1.0 (−0.4, 2.3)	0.1532	33.1 (10.7, 60.1)	0.0024

Models controlled for day of the week, daily mean relative humidity, daily mean air pressure, and time trend. AKI, acute kidney injury; CI, confidence interval.

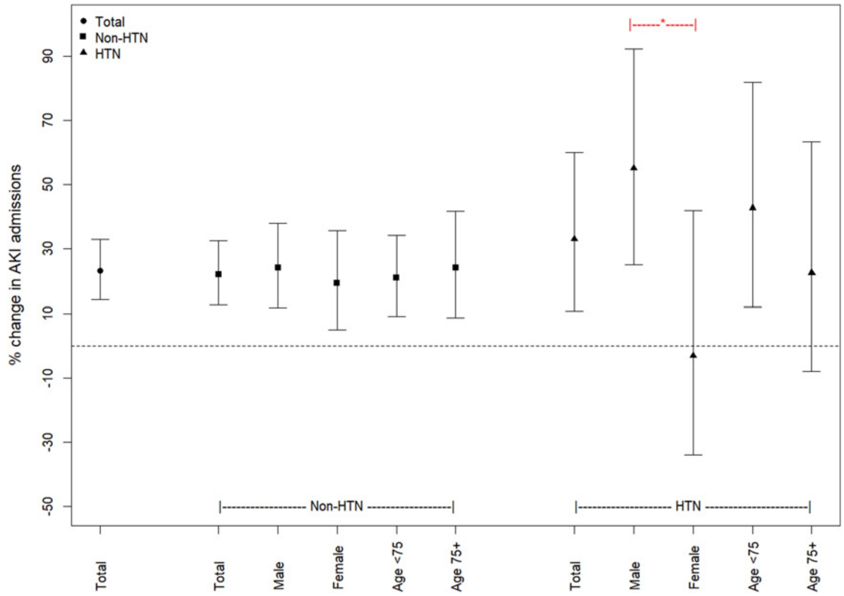

Fig. 2. Percentage change in risk of acute kidney injury admissions per 1 °C temperature increase above 28.8 °C in patients with and without hypertension. *Significant difference between groups at $\alpha = 0.05$. Models controlled for day of the week, daily mean relative humidity, daily mean air pressure, and time trend. HTN, with hypertension; Non-HTN, without hypertension.

wave periods, are crucial in preventing poor patient outcomes. The findings of this study also provide evidence for local governments to target specific populations vulnerable to high ambient temperatures.

Conflict of interests

The authors declare no conflict of interests.

Funding

This work was partially supported by the Women Scientist Research Program through the National Research Foundation of Korea (NRF) and funded by the Ministry of Science, ICT and Future Planning (No. 2015R1A1A3A04001325), the Korea Meteorological Administration Research and Development Program (No. KMIPA 2015-5120), and the Korea Centers for Disease Control and Prevention (No. 2017060C6C5). The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funders.

Acknowledgment

We thank the Health Insurance Review and Assessment Service (HIRA) for sharing health insurance claim data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2017.10.207.

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